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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/687,575	10/13/2000	Rima Kaddurah-Daouk	AVZ-007CP3	9336

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LAHIVE & COCKFIELD
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BOSTON, MA 02109

EXAMINER	
RAHMANI, NILOOFAR	

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 05/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/687,575	KADDURAH-DAOUK ET AL.	
	Examiner	Art Unit	
	Niloofar Rahmani	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 October 2000*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *86,91-96,98-100,108,113-118,120-122,133 and 134* is/are pending in the application.

4a) Of the above claim(s) *92,96,114 and 118* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *86,91,93-95,98-100,108,113,115-117,120-122,133-134* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 86, 91-96, 98-100, 108, 113-118, 120-122, and 133-134 are pending in the instant application. Claims 1-85, 87-90, 97, 101-107, 109-112, 119, and 123-132 are cancelled.

2. ***Election/Restrictions***

Applicant's election of Group 22 includes claims 86, 91-96, 98-104, 108, 113-118, and 120-126 in part, drawn to a method of treating Parkinson's or Huntington's disease in the reply filed on 01/23/2006 is acknowledged. Claims 86, 91, 93-95, 98-100, 108, 113, 115-117, 120-122, and 133-134 are examined. Claims 92, 96, 114, 118 remaining subject matter being drawn to the non-elected invention are withdrawn per 37 CFR 1.142(b). Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Priority

3. This application is filed on 10/13/2000, which is a CIP of application # 09/285,395, filed on 04/02/1999 (ABN), which is a CIP of 09/283,267, filed on 04/01/1999 (ABN), which claims benefit of 60/080,459, filed on 04/02/1998.

4. ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 86, 91, 93-95, 96, 98-100, 108, 113, 115-117, 120-122, and 133-134 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 86, 91, 93-95, 96, 98-100, 108, 113, 115-117, 120-122, and 133-134 are rejected because the terms "glutamate excitotoxicity, spin traps, growth factor, nicotinamide, ICE inhibitors, neuroimmunophilis, antioxidants, lipoic acid, cofactors, riboflavin, CoQ10" are ambiguous. What does it mean by these terms. Correction is required.

5. ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined

under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 86, 91, 93-95, 98, 100, 108,113, 115-117, 120-122, 133-134 are rejected under 35 U.S.C. 102(e) as being anticipated by Blass et al. of US 6,537,969, which disclosed the method for treating diseases of the nervous system include Parkinson's disease, Huntington's disease using the same pharmaceutical composition as the instant claims (See column 7, lines 10-13). Blass et al. disclosed the same pharmaceutical composition combining creatine and a neuroprotective agent as the instant claims (see column 5, lines 33-55). Therefore anticipation was found.

6. *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 99 is rejected under 103(a) as being unpatentable over Blass et al. of US 6,537,969.

Determination of the scope and content of the prior art (MPEP §2141.01)

Blass et al. generically disclosed pharmaceutical composition combining of creatine and a neuroprotective agent such as antioxidants, riboflavin, L-carnitine for treating Parkinson's disease, Huntington's disease (see column 5, lines 33-55).

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the instant claims and the prior art composition is that the prior art composition has 2 active ingredient combining creatine and a neuroprotective agent whereas the instant claimed composition has one additional neuroprotective agent or creatine compound.

Finding of prima facia obviousness-rational and motivation (MPEP §2142.2143)

One having ordinary skill in the art would be motivated to modify the pharmaceutical composition of Blass et al. by adding one additional neuroprotective agent or creatine compound to obtain the instant claims. Because additional neuroprotective agent or creatine compound can cause stronger ingredient activity.

7. *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 86, 91, 93-95, 98-100, and 133 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are eight factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

1) The breadth of the claims.
2) The nature of the invention,
3) The state of the prior art,
4) The level of one of ordinary skill,
5) The level of predictability in the art,
6) The amount of direction provided by the inventor,
7) The existence of working examples,
8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims: The claims ~~have~~ are drawn to treating Parkinson's disease using a therapeutically effective amount of a combination of creatine,

creatine phosphate or a creatine compound and a neuroprotective agent. This is narrow breadth of claims.

The nature of the invention: The instant invention is drawn to method for treating Parkinson's disease using pharmaceutical composition of a combination of creatine, creatine phosphate or a creatine compound and a neuroprotective agent.

The state of the prior art: The 3-NP (3-nitropropionic acid) model of Parkinson's disease is not predictable. "A primate model of striatonigral degeneration (SND), the neuropathology underlying levodopaunresponsive parkinsonism associated with multiple systemic atrophy, by sequential systemic administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 3-nitropropionic acid (3NP) in a Macaca fascicularis monkey. Chronic 3NP administration aggravated the motor symptoms and abolished the L-dopa response. In vivo magnetic resonance imaging revealed bilateral striatal lesions." (Ghorayeb et al., Movement Disorders, Vol. 15, pages 531-536).

The state of the prior art is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seeming high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The level of the skill in the art: The artisan using Applicants invention would be a physician with a MD degree and several years of experience.

The predictability in the art: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic effects, whether or not the pharmaceutical composition combining of creatine and a neuroprotective agent would be used for treating Parkinson's disease.

Amount of guidance/working examples: However, applicant has not guidance or examples for treating Parkinson's disease using pharmaceutical composition of a combination of creatine, creatine phosphate or a creatine compound and a neuroprotective agent. On page 8, lines 23-24 of the specification, applicant has example of activities of test compounds such as treating Parkinson's disease. On page 43, lines 25-36 of the specification, applicant discloses the formulation of the pharmaceutical composition comprising of creatine and a neuroprotective agent. On page 43, line 40 of the specification, applicant has example of doses up to 8 grams/day of creatine phosphate which administered to patients with cardiac diseases by intravenous injection. On page 54, line 36 to page 56, line 10 of the specification, applicant has mouse models of Parkinson's disease such as

MPTP, or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. On figure 4, the doses of using creatine and neuroprotective effects against MPTP measuring protein synthesis.

The quantity of experimentation needed: The quantity of experimentation is large because of the combination of two ingredients would have been to be formulated into a dosage form. The proper ratio and amount of these two ingredients found and this formulation tested in the clinic or in an assay known to be correlated to clinical efficacy. This is a large quantity of experimentation.

Taking all of the above into consideration, it is not seen where the instant claims 86, 91, 93-95, 98-100, and 133 for treating Parkinson's disease, have been enabled by the instant specification.

8. Claims 108, 113, 115-117, 120-122, 134 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are eight factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the

inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

1) The breadth of the claims.
2) The nature of the invention,
3) The state of the prior art,
4) The level of one of ordinary skill,
5) The level of predictability in the art,
6) The amount of direction provided by the inventor,
7) The existence of working examples,
8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims: The breadth of claims is drawn to treating Huntington's disease using a therapeutically effective amount of a combination of creatine, creatine phosphate or a creatine compound and a neuroprotective agent. Thus, the breadth of claims is modest.

The nature of the invention: The instant invention is drawn to method for treating Huntington's disease using pharmaceutical composition of a combination of creatine, creatine phosphate or a creatine compound and a neuroprotective agent.

The state of the prior art: The 3-NP (3-nitropropionic acid) model of Huntington's disease is not predictable. A number of animal models of Huntington's disease have been developed and characterized utilizing 3NP, however, these have typically suffered from heterogeneous outcomes. (Mitchell et al.,[2002],

<http://www.med.wayne.edu/neuroscience/labs/bird/Abstracts/Todd_ISMRM2002.pdf>). "Mitochondrial toxins like 3-nitropropionic acid (3-NP) and malonate, functioning as the inhibitors of the complex II of mitochondrial respiratory chain, have been found to effectively induce specific behavioral changes and selective striatal lesions in rats and non-human primates mimicking those in Huntington's disease." (Lee et al., progress in neurobiology, vol. 72, pages 87-110).

The state of the prior art is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seeming high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The level of the skill in the art: The artisan using Applicants invention would be a physician with a MD degree and several years of experience.

The predictability in the art: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic effects, whether or not the pharmaceutical

composition combining of creatine and a neuroprotective agent would be used for treating Huntington's disease.

Amount of guidance/working examples: However, applicant has not guidance or examples for treating Parkinson's disease using pharmaceutical composition of a combination of creatine, creatine phosphate or a creatine compound and a neuroprotective agent. On page 8, lines 23-24 of the specification, applicant has example of activities of test compounds such as treating Huntington's disease. On page 43, lines 25-36 of the specification, applicant discloses the formulation of the pharmaceutical composition comprising of creatine and a neuroprotective agent. On page 43, line 40 of the specification, applicant has example of doses up to 8 grams/day of creatine phosphate which administered to patients with cardiac diseases by intravenous injection. On pages 52, line 35 to page 54, line 9 of the specification, applicant has rat models of Huntington's disease using Malonate and 3-nitropropionic acid (3-NP). On figure 2-3, the doses of using creatine and neuroprotective effects against malonate are odd because there are not dose related.

The quantity of experimentation needed: The quantity of experimentation is large because of the combination of two ingredients would have been to be formulated into a dosage form. The proper ratio and amount of these two ingredients found and this formulation tested in the clinic or in an assay known to be correlated to clinical efficacy. This is a large quantity of experimentation.

Taking all of the above into consideration, it is not seen where the instant claims 108, 113, 115-117, 120-122, 134, for treating Huntington's disease, have been enabled by the instant specification.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Niloofar Rahmani whose telephone number is 571-272-4329. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thomas Mckenzie, can be reached on 571-272-0670. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NILOOFAR RAHMANI
05/24/2006
NR

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